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Comparison of antihypertensive efficacy of Atenolol, Metoprolol and Nebivolol in hypertensive Patients: a randomized trial

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Abstract:
Background: *Beta blockers are widely used as antihypertensive drugs in uncomplicated hypertension, especially, in patients with ischemic heart disease, stroke,arrhythmia and heart failure as they significantly reduce the risk which is well established.*
Aims and Objectives: *Aims of the study was to observe the effects of Atenolol, Metoprolol and Nebivolol on the arterial blood pressure along with their side effects and its Comparison of drugs used .*
Materials and methods: *In this randomized non blinded clinical trial on 148 selected patients. Patients were divided into three groups randomly. In group I patients (n=58) Atenolol, in group II patients (n=56) Metoprolol and in group III patients (n=34) Nebivolol was given. The BP was recorded monthly up to 6 month in same manner by standard mercury sphygmomanometer. The Mean arterial blood pressure (MAP), Systolic and diastolic presser was recorded. All data were collected and tabulated. Data is summarized and compared statistically by frequency distribution and percentage proportion. Chi square test and students t-test were applied to know the significant (p value) ratio of difference statistically by using software EpiCalc 2000.*
Result : *We found that after 6 months, the drug Nebivolol (Group III) significantly reduced the Systolic blood pressure (SBP) from 166.12±15.9 to 137.29±10.20, Diastolic blood pressure (DBP) from 97.24±9.93 to 83.06±4.33 and MAP from 119.60±8.08 to 101.14±6.01 in comparison to Group I& II . In the present study, only 6.08% patients (9/148) showed adverse drug reactions.*
Conclusion: *Nebivolol is a third generation beta adrenorecepter blocking drug with additional antioxidative properties. It has higher efficacy and tolerance compared to other beta adrenorecepter like Atenolol and Metoprolol.*

Keywords: *Hypertension, High Blood Pressure, Mean Arterial Pressure, Beta Adrenoreceptor*

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I. Introduction

Hypertension (HTN) or High Blood Pressure (HBP) is a long term medical condition where blood pressure (BP) in the arteries is persistently elevated [1]. Persistently elevated blood pressure is the major risk factor for coronary artery disease (CAD), stroke, heart failure, atrial fibrillation, peripheral vascular disease, vision loss, chronic kidney disease and dementia [2, 3, 4, 5]. High blood pressure is classified as primary (essential) hypertension and secondary hypertension [6]. In about 90-95% cases, essential hypertension is a major risk factor for CAD, cardiac failure and renal insufficiency due to lifestyle and genetic factors [6,7,8], while secondary hypertension contributes to 5-10% cases mainly due to identifiable underlying diseases [6]. Beta adreno-receptor blocker is the only drug which can be safely used in the treatment of cardiac as well as non-cardiac diseases. Beta -adrenoceptor (β-ARs) blocking agents (β -blockers) were first discovered in 1962 by Sir James Black at the Imperial Chemical Industries in the United Kingdom [9].

Beta - blockers prevent stimulation of β-1 receptor in the heart at nerve endings of sympathetic nervous system resulting in decreased heart rate and cardiac output, and β-2 receptor inhibition in bronchial smooth muscles results in broncho-constriction. On the other hand cardio selective β-Blockers are more potent on β-1 receptor than β-2 receptor thus reduces the risk of broncho-constriction. Three different types of β -receptors have been identified by molecular pharmacology: β1, β2, and β3 and are variably distributed in different tissues [10, 11]. β1 receptors are predominantly located in the heart and make up to 75% of all β -ARs, while β2 receptors are found in vascular and bronchial smooth muscle [12]. β3 receptors are located in the adipocytes where they are presumed to be involved in the fatty acid metabolism [13, 14]. In addition, β 3- ARs have been

described in cardiomyocytes, where they make up a population of about 5% of the β-AR [15], as well as in endothelial cells [16].

In the present era stress is a major cause of hypertension and it can be managed by life style modification, pharmacological treatment or both. Life style modification like; weight reduction in obese patients, increase in physical activity, avoidance of alcohol consumption and low sodium diet helps in decreasing the blood pressure and increases the efficacy of pharmaco-therapeutic regimens [17].

Pharmacological treatment includes management with one or more drug classes: thiazide diuretics, β blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE)–inhibitors, and angiotensin receptor blockers (ARBs). These medications can reduce BP as well as its complications [17, 18, and 19].

Although thiazide diuretics are recommended as the first-line therapy for most patients with HTN, β blockers have a compelling indication for use in patients with high-risk conditions such as heart failure, coronary heart disease (CHD) and diabetes [17,20]. Nebivolol is a novel, highly selective ß blocker with non adrenergic vasodilating properties. Nebivolol does not have ά 1 blocking properties and intrinsic sympathomimetic activity [21]. Reduction in BP and improvement in quality of life via/by reducing hypertensive complication is the major determinant of benefit provided by antihypertensive drugs [22].

Present study is designed to compare the effect of Nebivolol, a cardio selective β-blocker, with other β-blocker, on blood pressure especially the mean arterial pressure and its beneficial effect in tissue perfusion while reducing the chances of ischemia.

II. Aims And Objectives

Aims of the study are

1. Effects of Atenolol , Metoprolol and Nebivolol on the arterial blood pressure,.
2. Side effects of the drugs.
3. Comparative study of the drugs used in the study

III. Materials And Methods

It is a one and half years prospective observational study, (from June 2004 to November 2005) conducted in the department of pharmacology, S.S.M.C. Rewa and S.G.M Hospital Rewa M.P. During the study period all old (diagnosed) and new patients with HTN were included in the study. Written informed consent was taken from all the patients selected for the study. Selection of patients was done according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Table 1).

Table No. 1

Blood pressure classification	Systolic blood pressure in mm Hg	Diastolic blood pressure (DBP) in mm Hg
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Stage 1 Hypertension	140-159	or 90-99
Stage 2 Hypertension	> or =160	> or =100

SBP: Systolic blood pressur, DBP: Diastolic blood pressure

https://www.ncbi.nlm.nih.gov/books/NBK9630/

In this randomized non blinded clinical trial total 148 selected patients were divided into in three groups randomly. Patients who had history of rheumatic heart disease, stroke, recent myocardial infarction (<6month duration), allergic reaction to the drugs (Atenolol, Metoprolol and Nebivolol) and systolic hypertension > 200 mm of Hg were excluded from the study. Routine pathological, cardio-logical and radiological relevant investigations were done prior to select the cases.

In group I patients (n=58) Atenolol, in group II patients (n=56) Metoprolol and in group III patients (n=34) Nebivolol was given. The initial BP (systolic and diastolic) of the patients selected for the study was

recorded twice at 15 minutes interval in sitting position. The BP was recorded monthly up to 6 month in same manner by standard mercury sphygmomanometer. The Mean arterial blood pressure (MAP) was calculated by using formula below.

$$MAP = \frac{SBP + 2(DBP)}{3}$$

All data were collected and tabulated. Data is summarized and compared statistically by frequency distribution and percentage proportion. Chi square test and students t-test were applied to know the significant (*p* value) ratio of difference statistically by using software EpiCalc 2000.

IV. Results

A total 148 patients divided into three groups. Group I had n=58 (32.43%) patients, group II n=56 (37.84%) and in group III n=34 (22.97%), statistically significant (p= 0.027465) (Figure no. 1).

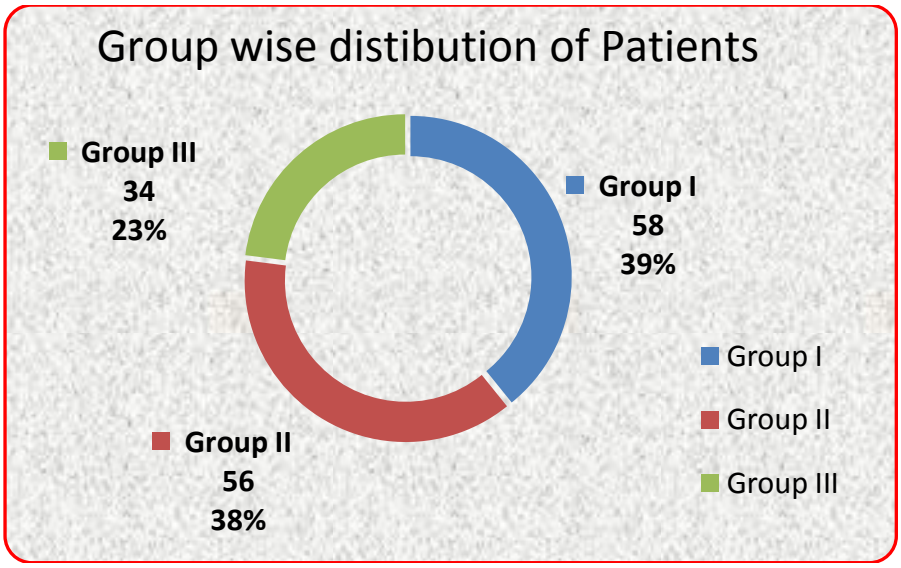

Fig no.1: Group wise Distribution of patients

Male to female ratio of the patients in the study was 81(54.73%) male and 67(45.27%) females. Group wise distribution of male and female was shown in Figure no. 2. How so ever male/ female distribution in the study was statistically insignificant (p= 0.249817)

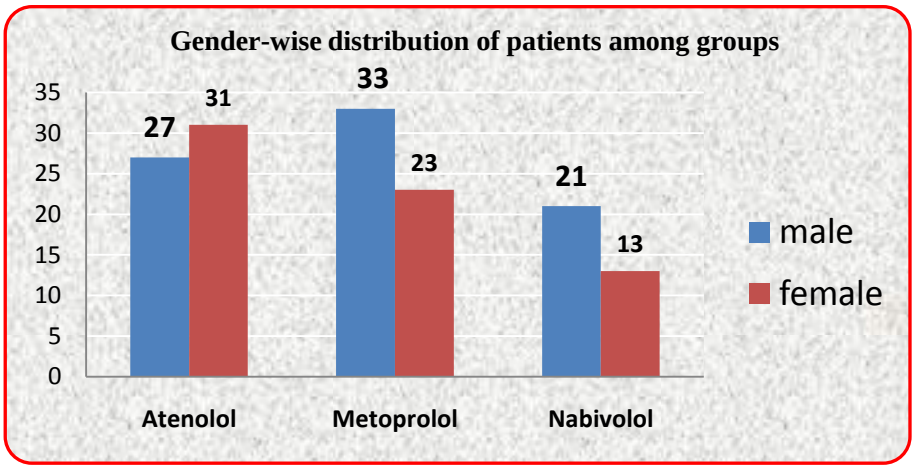

Figure No. 2: Gender-wise distribution of patients in different groups

The mean age of patients in the study was 45 years (age range from 25–65 years). In Group I patients, Atenolol 50 mg per day, Group II patients Metoprolol 50 mg per day and Group III patients Nebivolol 5 mg per day was given up to 6 months to control arterial blood pressure. We found that after 6 months, the drug Nebivolol (Group III) significantly reduced the Systolic blood pressure (SBP) from 166.12±15.9 to 137.29±10.20, Diastolic blood pressure (DBP) from 97.24±9.93 to 83.06±4.33 and MAP from 119.60±8.08 to 101.14±6.01 in comparison to Group I& II (Table No. 2). In the Group I reduction of SBP from 156.59±17.4 to 138.17±12.9, DBP from 91.83±10.1 to 83.55±5.59 and MAP from 113.24± 8.45 to 101.92±7.70, while in group II reduction in SBP (155.79±16.9 to 137.89±9.97), DBP from 99.36±8.17 to 83.96±4.55 and MAP (118.16±9.73 to 102.06±5.93).

Table No. 2: Gradual reduction of average fall of BP during study period

	Groups	Initial BP (mmHg)	After 1 month (mmHg)	After 3 month (mmHg)	After 6 month (mmHg)
Gradual reduction of mean systolic BP	I	156.59	8.29	8.9	1.24
	II	155.79	9.93	0.86	7.11
	III	166.12	18.18	8.06	2.59
Gradual reduction of mean diastolic BP	I	91.83	5.45	2.21	0.62
	II	99.36	8.15	3.45	3.79
	III	97.24	10.24	2.94	1
Gradual reduction of mean arterial BP	I	113.24	6.22	4.43	0.67
	II	118.16	8.55	2.86	4.69
	III	119.6	12.29	4.05	1.52

In the present study, only 6.08% patients (9/148) showed adverse drug reactions. Group wise distribution of adverse event was; In group I, 6.9 % (4/58) (bronchospasm, erectile dysfunction and fatigue), group II, 5.4% (3 /56) (nightmare and constipation) and in group III 5.9% (fatigue) patients were complaining of adverse drug reaction (Table No. 3).

Table no 3: Adverse drug reactions among groups

ADR	Group I (n=58)	Group II (n=56)	Group III (n=34)
CHF	0	0	0
Dizziness	0	0	0
Bradycardia	0	0	0
Nightmare	0	1	0
Bronchospasm	1	0	0
Diarrhoea	0	0	0
Depression	0	0	0
Postural hypotension	0	0	0
E. dysfunction	1	0	0
Constipation	0	2	0
Fatigue	2	0	2
Total	4	3	2

V. Discussion

The present study shows the effect of cardio-selective β blockers drugs i.e. Atenolol, Metoprolol and Nebivolol in mild to moderate hypertensive patients after 6 months. Brachial BP measurement is considered to be the best method for screening and diagnosing clinical hypertension. However, over recent years, assessment of CV (cardiovascular) risk in subjects with hypertension has led to development of more sophisticated methods of BP measurement, such as central BP [23]. Currently, several arguments suggest that central BP is more relevant than peripheral (brachial) BP for determining CV risk assessments [23 ,24, 25]. Few data are available on the comparative study of Atenolol , Metoprolol and Nebivolol in lowering blood pressure collectively (all together). But other studies are available where comparison is done between Nebivolol and other β blocker separately showing that Nebivolol is more efficacious and tolerable than other β blocker like Atenolol and Metoprolol, which also strengthens the results of present study.

Unlike other β blocker Nebivolol has vaso-dilating property that reduces systemic vascular resistance through nitric oxide [NO] release [21, 26]. Similarly reported by ; Uhlir et al 1991 in a study of Nebivolol 5 mg/day was compared with metoprolol 100 mg twice daily (BID) in 155 patients with mild-to-moderate essential hypertension. Target blood pressure was attained in 79% of nebivolol-treated patients and 66% of those in the metoprolol group. There were fewer adverse events reported by patients in the nebivolol group [27], In controlled clinical trials of Weber 2005 [28] nebivolol demonstrates a side effect profile similar to placebo, most notably in regards to side effects commonly associated with beta-blockers, such as fatigue and sexual dysfunction. Similarly reported by Doumas et al 2006 [29] in a recent clinical trial by studied in 29 out

of 44 hypertensive men who complained of erectile dysfunction while taking atenolol, metoprolol or bisoprolol. The researchers found that after switching to nebivolol therapy, 20 of the 29 noted significant improvement in erectile function without a significant change in BP. A study done by shahid A. et al (2014) in saudi also have similar results that nebivolol is more efficacious in lowering systolic , diastolic and mean arterial blood pressure than other beta adrenorecepter [30] .

It is well known that NO and its metabolites increase the activity of NO synthase (NO III) which in turn enhances NO release. Nebivolol itself inhibits NO degradation due to reactive oxygen species such as superoxide and its antioxidants property helps in maintaining normal function of endothelial cell, smooth muscle cell hypertrophy, platelet aggregation and adhesion. It also inhibits LDL (Low Density Lipoprotien) oxidation and Atherosclerotic plaque formation. Thus the function of the NO is to prevent hypertensive patients from ischemic complication. Nebivolol (5 mg) given to the patients reduces systolic, diastolic and mean arterial blood pressure more than Atenolol (50 mg) and Metoprolol (50 mg).

The result of the present study shows that Nebivolol is a unique drug which due to its vasodilatatory action and NO release property prevents hypertensive patients from ischemic complication and is also well tolerated by the patients.

VI. Conclusion

Nebivolol is a third generation beta adrenorecepter blocking drug with additional antioxidative properties. It has higher efficacy and tolerance compared to other beta adrenorecepter like Atenolol and Metoprolol. By reducing the peripheral vascular resistance it also plays a role in reducing the risk of ischemia. Tolerance of Nebivolol is due to its low dose and mild adverse reaction.

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